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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/587,468

Filing Date: November 27, 2006

Appellant(s): MORAZZONI ET AL

H. James Voeller
For Appellant

EXAMINER'S ANSWER

This is in response to the Appeal Brief filed 06/30/2011 appealing from the Office Action mailed 12/30/2010.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments after Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Physphatidylserine complex with Ginkgo	Physiologics	2003
EPA 0275005	Bombardelli	7-1988
Loew, Value of Ginkgo biloba in treatment of Alzheimer dementia, Wiener medizinische Wochenschrift (1946), (2002) Vol. 152, No. 15-16, pp. 418-22.		
Kim et al, Proteomics of neuroprotective actions of grape seed extract, FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp.		

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 23, 26, 29-40, and 46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Physiologics (Physiologics, Physphatidylserine complex with Ginkgo, 2003, online document provided as IDS by Applicant on 7/27/2006), in view of Bombardelli (EPA 0275005) (provided as IDS by Applicant on 7/27/2006).

This rejection is maintained for reasons of record set forth in the Office Action mailed out on 8/19/2010, repeated below. Applicants' arguments filed have been fully considered but they are not deemed to be persuasive.

Physiologics teaches dietary supplement of 60 soft gels (thus in the form of capsules/gels, thus the limitation of claim 30 is met, thus for oral administration, thus the limitation of claim 31 is met). Physiologics teaches phosphatidylserine complex with Ginkgo biloba is perfect for mild memory problems associated with aging (thus a method for the enhancement of cognitive function and alleviation of mental fatigue by improving the speed of memory and memory quality, by counteracting cognitive fatigue in normal and healthy persons, thus a method for the treatment of a disease related with the reduction of cognitive function, such as dementia or Alzheimer's disease). Physiologics teaches phosphatidylserine plays a role in neurotransmissions and supports cognitive function while Ginkgo biloba helps improve memory (col 1, 1st paragraph). Physiologics teaches phospholipid complex from soy lecithin standardized to contain 20% phosphatidylserine, 100 mg (thus a phospholipid containing 10-50%, 20-40%, or 20% of phosphatidylserine, thus the limitations of claims 23-25 are met). Physiologics teaches the product containing Ginkgo biloba extract 30 mg (standardized to contain 24% Ginkgo flavone glycosides) (thus at least 20% Ginkgo flavone) (3rd column, Supplement Facts). Thus the ratio between Ginkgo and the phosphatidylserine is about 1:3 (thus the limitations of claims 29 and 46 are met). Physiologics also teaches the product comprising 5 mg vitamin C (3rd column, Supplement Facts) (thus a pharmaceutically acceptable amount of at least one additive selected from vitamins, thus the limitation of claims 33 and 34 are met).

Physiologics does not teach forming a complex between Ginkgo and phosphatidylserine; neither does Physiologics teach the claimed dosage in claim 32.

Bombardelli teaches complex compounds of flavonoids with phospholipids, characterized by high lipophilia and improved bioavailability and therapeutic properties as compared with free, not complexed flavonoids. The complex compounds of the invention are suitable for use as the active principle in pharmaceutical and cosmetic (see Abstract). Bombardelli also teaches complex compounds of flavonoids with phospholipids (claim 1), wherein the phospholipids are selected from phosphatidyl serine, etc (claim 4), and wherein the flavonoids are selected from the group consisting of ginkgonetine, isoginkgonetine and bilobetine (claim 5), etc (thus Ginkgo biloba extract). Bombardelli also teaches the invention also provides a process for purifying flavonoids from plants such for example as Ginkgo biloba etc (page 3, 6th paragraph). Bombardelli further teaches the preparation of ginkgo biloba depurated extract /total soy phospholipids complex (page 10, Example 11).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to form a complex of Ginkgo biloba extract with phosphatidylserine in Physiologics since Bombardelli teaches complex of flavonoids and phospholipids has high lipophilia and it improves bioavailability; Bombardelli also teaches the preparation of ginkgo biloba extract and soy phospholipids complex as an example. Therefore, it would have been obvious for one of the ordinary skill in the art to form complex of Ginkgo biloba extract with soy phospholipid containing 20% phosphatidylserine in Physiologics to improve bioavailability so as to enhance cognitive function and alleviate of mental fatigue.

Regarding the limitation to the claimed dosage in claim 32, the result-effective adjustment in conventional working parameters is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. The differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990);

and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). see MPEP § 2144.05 part II A. Although the prior art did not specifically disclose the claimed dosage in claim 32, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine the dosage of phosphatidylserine complex with Ginkgo biloba because the amount of the claimed components is art-recognized result effective variables because it has the ability enhance memory function, which would have been routinely determined and optimized in the pharmaceutical art.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Claims 23, 26-41, and 46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Physiologics and Bombardelli as applied to claims 23, 26, 29-40, and 46 above, and further in view of Loew (Value of Ginkgo biloba in treatment of Alzheimer dementia, Wiener medizinische Wochenschrift (1946), (2002) Vol. 152, No. 15-16, pp. 418-22).

This rejection is maintained for reasons of record set forth in the Office Action mailed out on 8/19/2010, repeated below. Applicants' arguments filed have been fully considered but they are not deemed to be persuasive.

The teachings of Physiologics and Bombardelli are set forth above and applied as before.

The combination of Physiologics and Bombardelli do not specifically teach the principle active substance of Ginkgo biloba extract is bilobalide; the Ginkgo extract contains 2-10% terpene lactones, or the incorporation of acetylcholinesterase inhibitor into the composition.

Loew teaches Ginkgo biloba special extract Egb 761 is a standardized and highly purified extract of Ginkgo leaves. Among the active constituents are the ginkgo-flavone glycosides and the terpene-lactones (ginkgolides, bilobalide). The presence of these constituents in Ginkgo extracts, which constituents are known to be useful for treating Alzheimer's disease, provides the rationale for clinical trials in vascular dementia and primary degenerative dementia of the Alzheimer's disease, and in mixed forms of both. In clinical trials of different working-groups, effects of Ginkgo biloba on the cognitive performance, global function, and activities of the daily living have been found. Metaanalysis in the indication—demential disorders--comparing Ginkgo biloba versus acetylcholinesterase inhibitors have shown a similar clinical efficacy of both therapy regimens with an additional drug safety benefit for Ginkgo. Loew further teaches that clinical trials with fixed combinations of acetylcholinesterase inhibitors with Ginkgo biloba extracts in moderate or severe dementia would be necessary (see Abstract).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the ginkgo-flavone glycosides and 2-10% terpene-lactones (ginkgolides, bilobalide) from Loew in the enhancement of cognitive function as Loew explicitly teaches Ginkgo biloba extract contains those components. It would have been *prima facie* obvious for one of ordinary skill in the art to include acetylcholinesterase inhibitors in the composition since Loew teaches Ginkgo biloba has shown a similar clinical efficacy with acetylcholinesterase inhibitors, and clinical trials with fixed combinations of acetylcholinesterase

inhibitors with Ginkgo biloba extracts in moderate or severe dementia would be necessary (see Abstract).

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Claims 23, 26, 29-40, 42, and 46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Physiologics and Bombardelli as applied to claims 23, 26, 29-40, and 46 above, and further in view of Kim et al (Kim et al, Proteomics of neuroprotective actions of grape seed extract, FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp.).

This rejection is maintained for reasons of record set forth in the Office Action mailed out on 8/19/2010, repeated below. Applicants' arguments filed have been fully considered but they are not deemed to be persuasive.

The teachings of Physiologics and Bombardelli are set forth above and applied as before.

The combination of Physiologics and Bombardelli do not specifically teach the incorporation of grape seed extract into the composition.

Kim et al teach certain botanicals are purported to have health benefits because of antioxidant activity intrinsic to their polyphenol content. Grape seed extract (GSE) preparations, enriched in the proanthocyanidins, are in this category. Animal behavior studies showed that dietary supplementation with blueberry extract, enriched in proanthocyanidins similar to those in GSE, protected against age-related cognitive decline (see Abstract).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to incorporate the grape seed extract from Kim et al into the composition of Physiologics since Kim et al teach Grape seed extract (GSE) preparations, enriched in the proanthocyanidins, protected against age-related cognitive decline. Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to incorporate the grape seed extract from Kim et al into the composition of Physiologics for the enhancement of cognitive function.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Appellants summarize what Physiologics teaches. Regarding Bombardelli, Appellants state that “BOMBARDELLI determined that these “complex compounds” possess higher bioavailability for topical formulations. In topical applications, the compounds were 2-4 times as active as the substances administered in free form (see, col. 3, lines 23- 27). In particular, BOMBARDELLI discloses that a complex of *Ginkgo biloba* and phosphatidyl choline had improved vasodilatory activity (see, Table i) and improved antiedematous activity (see, Table 2) when topically applied. BOMBARDELLI then suggests that the compounds could provide increased blood flow at the cutaneous level and may be useful in cosmetic applications. BOMBARDELLI further suggests that the flavonoids may have fibroblast proliferation

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stimulating activity and therefore may be useful in dermatology for ulcer healing and in cosmetic treatments such as collagen production (see, col. 4, lines 1-7)" (page 8, 2nd paragraph).

This is not found persuasive. Bombardelli explicitly teaches "on the contrary, the compounds of flavonoids with phospholipids, subject of the invention, thanks to their lipophile character, are perfectly absorbed through oral administration and increases the therapeutic effectiveness of the flavonoids both by oral and parenteral or topical administration (page 2, lines 30-32). Bombardelli also teaches capsules containing *Ginkgo biloba* complex (page 12, Example 17). Thus, Bombardelli not only teaches topical application, but also teaches oral administration of complex compounds of flavonoids with phospholipids. .

Appellants argue that "BOMBARDELLI fails to teach or suggest, however, that flavonoids would have any effect on enhancing cognitive functions or alleviating mental fatigue, or for improving memory speed and memory quality, or for treating any disease related to reduced cognitive function and increased mental fatigue, which is the featured subject matter of the present claims. More particularly, BOMBARDELLI fails to recognize that a complex of *Ginkgo biloba* extract with phosphatidylserine has any significant effects above a complex of ginkgo-phosphatidylcholine" (page 8, last paragraph). Appellants also argue that "One of ordinary skill in the art, in view of the teachings of PHYSIOLOGICS and BOMBARDELLI, would have no reason to select a complex of ginkgo-phosphatidylserine in order to achieve the desired therapeutic purpose - enhancing cognitive function and alleviating mental fatigue, improving memory speed and memory quality, reducing deterioration of memory speed and memory quality, or treating a disease related to reduced cognitive function and increased mental fatigue. Indeed, applicants have demonstrated that a complex of ginkgo- phosphatidylserine

provides superior results in cognitive function when compared to the complex of ginkgo-phosphatidylcholine disclosed in BOMBARDELLI” (page 9, 1st paragraph). Appellants further argue that “Indeed, BOMBARDELLI includes only a single specific reference to phosphatidylserine in the entire disclosure, and that is in the claims. In claim 1, BOMBARDELLI lists phosphatidylserine as one of a list of possible phospholipids that includes soy lecithin, egg lecithin, phospholipids from bovine or swine brain or dermis, phosphatidyl choline, and phosphatidyl ethanolamine. Claim 1 also features an extensive list of the various possible flavonoids to use in the complex combination. Then, in the Examples, BOMBARDELLI includes complexes of phosphatidylcholine and phosphatidylethanolamine (see, Examples 1-12) but fails to include any examples of a complex with phosphatidylserine. Thus, BOMBARDELLI fails to teach or suggest anything that would have led one of ordinary skill in the art to expect the superior results obtained specifically from the complex of phosphatidylserine with ginkgo, for the cognitive and mental treatment methods featured in the present claims” (page 11, 2nd paragraph).

This is not found persuasive. Bombardelli teaches complex compounds of flavonoids with phospholipids, characterized by high lipophilia and improved bioavailability and therapeutic properties as compared with free, not complexed flavonoids. The complex compounds of the invention are suitable for use as the active principle in pharmaceutical and cosmetic (see Abstract). Bombardelli also teaches complex compounds of flavonoids with phospholipids (claim 1), wherein the phospholipids are selected from phosphatidyl serine, etc (claim 4), and wherein the flavonoids are selected from the group consisting of ginkgonetine, isoginkgonetine and bilobetine (claim 5), etc (thus Ginkgo biloba extract). Bombardelli also teaches the invention

also provides a process for purifying flavonoids from plants such for example as Ginkgo biloba etc (page 3, 6th paragraph). Bombardelli further teaches the preparation of ginkgo biloba depurated extract /total soy phospholipids complex (page 10, Example 11). It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to form a complex of Ginkgo biloba extract with phosphatidylserine in Physiologics since Bombardelli teaches complex of flavonoids and phospholipids has high lipophilia and it improves bioavailability; Bombardelli also teaches the preparation of ginkgo biloba extract and soy phospholipids complex as an example. Therefore, it would have been obvious for one of the ordinary skill in the art to form complex of Ginkgo biloba extract with soy phospholipid containing 20% phosphatidylserine in Physiologics to improve bioavailability so as to enhance cognitive function and alleviate of mental fatigue.

Appellants argue that “As detailed in the present specification, in the cognitive assessment tests and results section, a complex of *Ginkgo biloba* extract with phosphatidylserine has outstanding effectiveness compared to both the non-complexed ginkgo as well as to a complex of ginkgo-phosphatidylcholine. (See, Quality of Memory, Picture Recognition Accuracy, Speed of Memory, Timed Memory Tasks, and other tasks concerning attention, page 16, line 16 to page 29, line 5; and Figures 1-6, reproduced below). Crucially, in essentially every aspect tested, the complex of ginkgo-phosphatidylserine performed better than the complex of ginkgo-phosphatidylcholine” (page 9, last paragraph). Appellants also argue that “One of ordinary skill in the art, in view of the teachings of PHYSILOGICS and BOMBARDELLI, would have no reason to select phosphatidylserine in order to achieve the desired therapeutic purpose - enhancing cognitive function and alleviating mental fatigue, improving memory speed

and memory quality, reducing deterioration of memory speed and memory quality, or treating a disease related to reduced cognitive function and increased mental fatigue. Applicants have demonstrated that a complex of ginkgo phosphatidylserine provides superior results in cognitive function when compared to the complex of ginkgo-phosphatidylcholine disclosed in BOMBARDELLI" (page 10, last paragraph bridging page 11). Appellants further argue that "Further support for the unexpectedly superior results of a complex of ginkgo with phosphatidylserine is provided in the Rule 132 Declaration of Ezio Bombardelli, which is of record and was submitted with the May 29, 2009, Amendment. The Declaration includes the results of experiments carried out on 15 subjects, each subject treated with capsules respectively containing: *Ginkgo biloba* extract (GBE); phospholipids containing 20% phosphatidylserine (PS); mechanical mixtures containing *Ginkgo biloba* extract and phosphatidylserine (GBE + PS); and complexes of *Ginkgo-phosphatidylserine* (Complex). The results show that capsules containing the complex of *Ginkgo* with phosphatidylserine show a remarkably higher and statistically meaningful activity than that of capsules filled with *Ginkgo biloba* extract, phosphatidylserine, or mixtures of *Ginkgo biloba* extract and phosphatidylserine. The results of Speed of Memory tests from the Declaration are reproduced in the following graph" (page 11, last paragraph bridging page 12). Appellants conclude that "Thus, the presently claimed methods for enhancing cognitive function, alleviating mental fatigue, improving memory speed and memory quality, reducing deterioration of memory speed and memory quality and treating diseases related to reduced cognitive function and mental fatigue, by administering a complex of ginkgo with phosphatidylserine would not have been obvious to one of ordinary skill in the art from the teachings of BOMBARDELLI" (page 12, last paragraph bridging page 13).

This is not found persuasive. The allegedly “unexpected results” was totally expected, as the cited two references foretell the results. First of all, Physiologics teaches that phosphatidylserine complex with Ginkgo biloba is perfect for mild memory problems associated with aging. Physiologics teaches phosphatidylserine plays a role in neurotransmissions and supports cognitive function while Ginkgo biloba helps improve memory. Physiologics also teaches the claimed concentration of (20%) of the complex, which was used in the Declaration for showing “unexpected results”. Even though the formation of the phosphatidylserine complex with Ginkgo biloba in Physiologics is not exactly the same as described in the current Specification, the second reference Bombardelli teaches complex compounds of flavonoids with phospholipids, characterized by high lipophilia and improved bioavailability and therapeutic properties as compared with free, not complexed flavonoids complex compounds of flavonoids with phospholipids (see claim 1), wherein the phospholipids are selected from phosphatidyl serine, etc (claim 4), and wherein the flavonoids are selected from the group consisting of ginkgonetine, isoginkgonetine and bilobetine (claim 5), etc (thus Ginkgo biloba extract). Bombardelli also teaches the invention also provides a process for purifying flavonoids from plants such for example as Ginkgo biloba etc (page 3, 6th paragraph). Bombardelli further teaches complex of flavonoids and phospholipids has high lipophilia and it improves bioavailability. Therefore, it would have been obvious for one of the ordinary skill in the art to form complex of Ginkgo biloba extract with soy phospholipid containing 20% phosphatidylserine in Physiologics to improve bioavailability so as to enhance cognitive function and alleviate of mental fatigue. Thus, the “unexpected results” is expected, and the rejections are maintained for the above reasons.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Qiuwen Mi

July 5, 2011

Conferees:

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